SCIENTIFIC ABSTRACT

Phase I/IB Study of Immunization with Autologous Tumor Cells Transfected with The GM-CSF Gene by Particle-Mediated Transfer in Patients with Melanoma or Sarcoma.

The objective of this Phase I study is to assess the acute and long-term toxicities of intradermal vaccination of cancer patients with lethally-irradiated tumor cells that have been transfected by particle-mediated gene transfer (PMGT) with gold particles coated with human granulocyte-macrophage colony stimulating factor (GM-CSF) DNA in a plasmid expression vector. The GM-CSF DNA-coated gold particles are delivered to tumor cells using helium pressure with a hand held gene delivery device. Preclinical studies have demonstrated that vaccination of mice with irradiated, GM-CSF-transfected melanoma cells provided protection from subsequent challenges with non-irradiated, non-transfected tumor cells. Ongoing human tumor immunotherapy studies use patients' melanoma or renal carcinoma cells transfected with a retroviral vector containing GM-CSF cDNA as a vaccine to elicit anti-tumor immune responses. PMGT transfection, unlike retroviral transfection, does not require tumor cells to proliferate *in vitro* to undergo gene transfer. Instead, tumor tissue can be dissociated into small tissue clumps or cell aggregates and then immediately transfected using the gene gun. PMGT physically inserts the DNA without the need for cell surface interaction with viral components or exposure of the patient to viral antigens. As described in this protocol, fresh human sarcoma and melanoma specimens can be transfected with the GM-CSF DNA-coated gold particles with subsequent production of biologically active GM-CSF protein.

In this study tumor tissue will be obtained from patients with melanoma or sarcoma. Tumor tissue will be dissociated, irradiated, and transfected with GM-CSF DNA by PMGT. In this ascending dosage study, two dose levels of GM-CSF DNA will be studied in 2 groups of 6 patients each. Patients will receive two intradermal injections of the irradiated, transfected tumor in a single extremity. On days 3 and 14 post-vaccination, patients will undergo surgical excision of the vaccination sites to assess GM-CSF production and infiltration of immune effector cells. On Day 25, patients will undergo DTH testing with intradermal injection in their opposite extremity of 5×10^6 irradiated non-transfected autologous tumor cells cryopreserved at the time of vaccine preparation. This injection site will be assessed on day 28 post-vaccination and surgical excision of the DTH testing site will be performed on day 28 if a positive reaction is noted. The patients will be observed for local and systemic toxicity on days 2, 3, 5, 8, 14, 25, and 28 after the vaccination. Restaging of the patients' disease and long term toxicity evaluation will be performed at 3, 6, and 12 months and then yearly.